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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,596	08/19/2003	Robert C. Getts	4081.011.400	3977

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EXAMINER

SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
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1634

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/643,596	Applicant(s) GETTS, ROBERT C.	
	Examiner Bradley L. Sisson	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 December 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 23-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities: A review of the disclosure finds that, on the left margin, the first 3 or 4 letters of all lines are missing or are partially obliterated.
2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
5. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). . . . We have held that a patent specification complies with the statute

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even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

6. For purposes of examination, claims 23, 31, 32, and 35-39 have been construed as not requiring any detection step be performed, and that no useful information is being derived from the "assay." Support for this interpretation is predicated on the requirement of a dependent claim further limiting the claim from which it depends. Given that claims 24-30, 33, and 34 all recite some form of detection, claims 23, 31, 32, and 35-39 do not and cannot. Accordingly, the rejection is based on the aspect that claims 23, 31, 32, and 35-39 do not result in any useful information, and as such do not have utility under 35 USC 101 (see below), and therefore cannot be enabled by the disclosure..

The quantity of experimentation necessary.

The quantity of experimentation is considerable, on the order of several man-years, with no reasonable expectation of success.

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The amount of direction or guidance presented.

The specification incorporates by reference patents at page 9 of the specification that disclose dendrimers, and provides general guidance as to how an assay can be conducted.

The presence or absence of working examples.

The specification provides two examples: Example 1, pages 34-39; and Example 2, pages 39-47.

Neither example teaches how any useful information is obtained when no detecting step is performed.

The nature of the invention.

The claimed invention relates directly to matters of chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The predictability or unpredictability of the art

Zhang et al., *Bioinformatics*, Vol. 19, No. 1, 2003, page 14, states:

It is widely recognized that the hybridization process is prone to errors and that the future of DNA sequencing by hybridization is predicated on the ability to successfully cope with such errors. However, the occurrence of hybridization errors results in the computational difficulty of the reconstruction of DNA sequencing by hybridization. The reconstruction problem of DNA sequencing by hybridization with errors is a strongly NP-hard problem. So far the problem has not been solved well.

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Chan (US Patent Application Publication US 2002/0119455 A1):

[0018] In practice, Probe Up methods have been used to generate sequences of about 100 base pairs. Imperfect hybridization has led to difficulties in generating adequate sequence. Error in hybridization is amplified many times. A 1% error rate reduces the maximum length that can be sequenced by at least 10%. Thus if 1% of 65,536 oligonucleotides gave false positive hybridization signals when hybridizing to a 200-mer DNA target, 75% of the scored "hybridizations" would be false (Bains, 1997). Sequence determination would be impossible in such an instance. The conclusion is that hybridization must be extremely effective in order to generate reasonable data. Furthermore, sequencing by hybridization also encounters problems when there are repeats in sequences that are one base less than the length of the probe. When such sequences are present, multiple possible sequences are compatible with the hybridization data. (Emphasis added.)

As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

- The purity of the nucleic acid preparation.
- Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
- Length of homologous base sequences- any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
- Ionic strength- the rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

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- Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.
- Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
- Denaturing reagents- the presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.
- Incubation- the longer the incubation time, the more complete will be the hybridization.
- Volume exclusion agents- the presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.
- Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed non-enabled by the disclosure.

Barany et al. (US 2007/0042419 A1), at paragraph 0036 teaches in part:

For allele-specific oligonucleotide hybridization ("ASO"), the mutation must be known, hybridization and washing conditions must be known, cross-reactivity is difficult to prevent, closely-clustered sites due to interference of overlapping primers cannot undergo multiplex detection, and mutant DNA cannot be detected in less than 5% of background of normal DNA.

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Choi et al. (US 2007/0042400 A1), at paragraph 0035, teach:

[0035] In conventional methods of preparing nucleic acid, polysaccharides such as starch often co-precipitate with nucleic acid. When polysaccharides co-precipitate with nucleic acid, it is difficult to manipulate nucleic acids by amplification methods, such as PCR, or by other detection methods, such as hybridization detection. Polysaccharides may also inhibit digestion with restriction endonucleases and other enzymatic manipulations.

It is noted that the claimed method fairly encompasses the use of genomic DNA, and the use of an enzyme substrate as a label.

Yasuno et al., (US 2007/0031829 A1), paragraph 0037, teach in part:

Certain oligonucleotides hybridize to polynucleotides having complementary sequences. Although DNA hybridization is sequence-specific, it is difficult to completely exclude hybridizations towards very similar nucleotide sequences.

Wang et al., (US 2007/0009954 A1), teach:

[0004] A number of methods have been developed to score SNPs, including allele-specific hybridization, electrophoretic DNA sequencing, single-nucleotide extension using labeled chain terminators, the "Invader" assay (Third Wave Technologies, Madison Wis.), mass spectrometry, the 5' nuclease assay (Taqman; see below), etc. All of these methods entail assays that are either difficult or expensive to develop, or difficult or expensive to perform.

Rowlen et al., (US 2006/0286570 A1) teach:

[0004] A variety of methods exist for detection of molecular recognition events. Detection of molecular recognition events such as DNA hybridization, antibody-antigen interactions, and protein-protein interactions becomes increasingly difficult as the number of recognition events to be detected decreases.

It is noted that the claimed method places no lower limit on the ability to accurately and reproducibly detect any binding between polymer and unit specific markers.

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As evidenced above, the art is replete with known issues that directly impact the enablement of the claimed invention. A review of the instant disclosure fails to identify how these art-recognized issues are to be overcome such that the full scope of the invention can be practiced without the public having to resort to undue experimentation.

The breadth of the claims

The claims encompass performing an hybridization reaction where no signal is detected and no useful information is obtained. The claims have sufficient breadth of scope so to encompass the hybridization between any target and probe, the sequencing of nucleic acids via hybridization, detection of point mutations, and in short, all of the embodiments from which art-recognized issues of unpredictability are known to exist.

It is further noted that claim 34 calls for the use of three channels so to detect signals from three different nucleic acids. However, claim 23, from which it depends, only provides for two labels that could be detected, not three that would enable the use of three detection channels.

Accordingly, it is not possible to detect a third signal when such is never added or introduced into the reaction.

7. In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

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8. Claims 23, 31, 32, and 35-39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

9. For purposes of examination, claims 23, 31, 32, and 35-39 have been construed as not requiring any detection step be performed, and that no useful information is being derived from the "assay." Support for this interpretation is predicated on the requirement of a dependent claim further limiting the claim from which it depends. Given that claims 24-30, 33, and 34 all recite some form of detection, claims 23, 31, 32, and 35-39 do not and cannot. Accordingly, the rejection is based on the aspect that claims 23, 31, 32, and 35-39 do not result in any useful information, and as such do not have utility under 35 USC 101.

10. Claims 23, 31, 32, and 35-39 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 23-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. As presently worded, the claims are amended such that it is not clear what the objective of the assay is. Not knowing what the objective is, one cannot readily determine the metes and

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bounds the method is to be applied to, and cannot also readily determine if the recited method steps render the claim complete.

14. Claims 23, 31, 32, and 35-39 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The detection of some meaningful signal from the assay so that a determination of the target being present or not can be made.

15. Claim 34 is confusing as to how one can detect a third signal when reagents have been recited that only allow for the detection of signals using two channels.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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18. Claims 23-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,057,410 (Kawasaki et al.), in view of US 2004/0219569 A1 (Yehiely et al.), US Patent 5,508,188 (Barsky et al.) and US Patent 6,110,687 (Nilsen).

19. Kawasaki et al., column 14, discloses stripping blots and rehybridizing the immobilized sequences so to detect yet other nucleic acid sequences of interest.

20. Yehiely et al., paragraph 0234, teaches stripping and reuse of a microarray hybridization reaction.

21. Barsky et al., column 8, disclose conditions under which blots were stripped of a hybridized probe such that they could be reused in subsequent hybridization reactions.

22. Nilsen teaches at length the use of dendrimers as a probe for the detection of target sequences.

23. It would have been obvious to one of ordinary skill in the art to combine the methods of Kawasaki et al., Yehiely et al., Barsky et al., and Nilsen as Kawasaki et al., Yehiely et al., and Barsky et al., all teach the stripping of a probe from a blot or microarray such that the blot or microarray could be reused in a subsequent hybridization reaction. Said ordinary artisan would have been motivated to apply the method to where dendrimers are being used in an assay as the binding kinetics is the same as traditional probes, yet affords the ordinary artisan with markedly increased sensitivity.

24. In view of the wide applicability, the detailed teachings, said ordinary artisan would have had a most reasonable expectation of success, and in view of the ability to save financial resources by reusing blots and/or microarrays, said ordinary artisan would have been highly motivated.

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25. Therefore, and in the absence of convincing evidence to the contrary, claims 1-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,057,410 (Kawasaki et al.), in view of US 2004/0219569 A1 (Yehiely et al.), US Patent 5,508,188 (Barsky et al.) and US Patent 6,110,687 (Nilsen).

Response to argument

26. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the removal of the dendrimer while retaining probes annealed to immobilized target sequences) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

27. At page 10, bridging to page 11 of the response, argument is presented that the invention satisfies long-felt need, and provides "greater efficiency and ease of reuse of blots and microarrays in a manner which was not previously appreciated. This argument has been fully considered and has not been found persuasive. Attention is directed to MPEP 2145.

Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.

The arguments of counsel cannot take the place of evidence in the record. In *re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In *re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

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28. For the above reasons,, and in the absence of convincing evidence to the contrary, claims 23-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,057,410 (Kawasaki et al.), in view of US 2004/0219569 A1 (Yehiely et al.), US Patent 5,508,188 (Barsky et al.) and US Patent 6,110,687 (Nilsen).

Conclusion


29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

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like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS